Effective Shared Care Agreement (ESCA)

Rufinamide

ESCA: Adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years of age and older

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of rufinamide for epileptic seizures can be shared between the specialist and general practitioner (GP). You are invited to participate however, if you do not feel confident to undertake this role, then you are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care will be explained to the patient by the specialist initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with for epileptic seizures are usually under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

RESPONSIBILITIES and ROLES

Specialist responsibilities
1. Confirm the diagnosis of epileptic seizures in Lennox-Gastaut syndrome
2. Discuss the potential benefits, treatment side effects, and possible drug interactions with the patient
3. Ask the GP whether he or she is willing to participate in shared care before initiating therapy so that appropriate follow on prescribing arrangements can be made
4. Do baseline monitoring prior to initiation of rufinamide
5. Initiate treatment and stabilise dose of rufinamide
6. Review the patient's condition and monitor response to treatment regularly
7. A written summary to be sent promptly to the GP i.e. within 10 working days of a hospital outpatient review or inpatient stay
8. Report serious adverse events to the MHRA
9. Ensure clear backup arrangements exist for GPs, for advice and support (Please complete details below)

General Practitioner responsibilities						
1. Reply to the request for shared care as soon as practicable i.e. within 10 working days						
2. Prescribe rufinamide at the dose recommended						
3. In the patient's notes, using the appropriate Read Code listed below, denote that the patient is receiving treatment under a shared care agreement						
GP Prescribing System	**Read Code**	**Description**		**GP Prescribing System**	**Read Code**	**Description**
EMIS and Vision	8BM5.00	Shared care prescribing		SystmOne	XaB58	Shared care
4. Monitor patient's response to treatment; make dosage adjustments if agreed with specialist						
5. Report to and seek advice from the specialist or clinical nurse specialist on any aspect of patient care that is of concern to the GP, patient or carer and may affect treatment						
6. Refer back to specialist if condition deteriorates						
7. Report serious adverse events to specialist and MHRA						
8. Stop treatment on advice of specialist						

Patient's role
1. Report to the specialist, clinical nurse specialist or GP if he or she does not have a clear understanding of the treatment
2. Share any concerns in relation to treatment with rufinamide with the specialist, clinical nurse specialist or GP
3. Report any adverse effects to the specialist or GP whilst taking rufinamide
4. Attend regular outpatient appointments with the specialist

BACK-UP ADVICE AND SUPPORT

Trust	Contact details	Telephone No.	Email address:
	Consultant:-		
	Specialist Nurse		

SUPPORTING INFORMATION

<table>
<tr><td>Indication</td><td>Adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years of age and older</td></tr>
<tr><td>Dosage and Administration</td><td>
<u>Use in children four years of age or older and less than 30 kg</u>
Patients <30 kg not receiving valproate:
Treatment should be initiated at a daily dose of 200 mg (5 ml dosing suspension given as two 2.5 ml doses, one in the morning and one in the evening). According to clinical response and tolerability, the dose may be increased by 200 mg/day increments, as frequently as every two days, up to a maximum recommended dose of 1000 mg/day (25 ml/day). Doses of up to 3600 mg/day (90 ml/day) have been studied in a limited number of patients.

Patients <30 kg also receiving valproate:
As valproate significantly decreases clearance of rufinamide, a lower maximum dose of rufinamide is recommended for patients <30 kg being co-administered valproate. Treatment should be initiated at a daily dose of 200 mg. According to clinical response and tolerability, after a minimum of 2 days the dose may be increased by 200 mg/day, to the maximum recommended dose of 600 mg/day (15 ml/day).

<u>Use in adults, adolescents and children four years of age or older of 30 kg or over</u>
Treatment should be initiated at a daily dose of 400 mg (10 ml dosing suspension given as two 5 ml doses). According to clinical response and tolerability, the dose may be increased by 400 mg/day increments, as frequently as every two days, up to a maximum recommended dose as indicated in the table below.
<table>
<tr><td>Weight range</td><td>30.0 – 50.0 kg</td><td>50.1 – 70.0 kg</td><td>≥70.1 kg</td></tr>
<tr><td>Maximum recommended dose</td><td>1,800 mg/day or 45 ml/day</td><td>2,400 mg/day or 60 ml/day</td><td>3,200 mg/day or 80 ml/day</td></tr>
</table>
Doses of up to 4,000 mg/day (100 ml/day) in the 30-50 kg range or 4,800 mg/day (120 ml/day) in the over 50 kg category have been studied in a limited number of patients.

<u>Discontinuation of treatment</u>
When rufinamide treatment is to be discontinued, it should be withdrawn gradually. In clinical trials rufinamide discontinuation was achieved by reducing the dose by approximately 25% every two days.
In the case of one or more missed doses, individualised clinical judgement is necessary.
Uncontrolled open-label studies suggest sustained long-term efficacy, although no controlled study has been conducted for longer than three months.

<u>Paediatric population</u>
The safety and efficacy of rufinamide of children aged 4 years and less have not yet been established. No data are available.

<u>Older people</u>
There is limited information on the use of rufinamide in older people. Since, the pharmacokinetics of rufinamide are not altered in older people, dosage adjustment is not required in patients over 65 years of age.
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<tr><td>Renal Impairment</td><td>Mild
Moderate
Severe</td><td>No dose adjustments are required</td></tr>
<tr><td>Hepatic impairment</td><td>Mild
Moderate</td><td>Caution and careful dose titration is recommended</td></tr>
<tr><td></td><td>Severe</td><td>Not recommended</td></tr>
<tr><td>Contra-indications / Special precautions</td><td>
Contra-Indications:
Hypersensitivity to the active substance, triazole derivatives or to any of the excipients
Caution
Status epilepticus

Status epilepticus cases have been observed during clinical development studies, under rufinamide whereas no such cases have been observed under placebo. These events led to rufinamide discontinuation in 20 % of the cases. If patients develop new seizure types and/or experience an increased frequency of status epilepticus that is different from the patient's baseline condition, then the benefit risk ratio of the therapy should be reassessed.

Withdrawal of rufinamide

Rufinamide should be withdrawn gradually to reduce the possibility of seizures on withdrawal. In clinical studies discontinuation was achieved by reducing the dose by approximately 25% every two days. There are insufficient data on the withdrawal of concomitant antiepileptic medicinal products once seizure control has been achieved with the addition of rufinamide.

Central Nervous System reactions

Rufinamide treatment has been associated with dizziness, somnolence, ataxia and gait disturbances, which could increase the occurrence of accidental falls in this population. Patients and carers should exercise caution until they are familiar with the potential effects of this medicinal product.

Hypersensitivity reactions
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<tr><td></td><td colspan="2">
Serious antiepileptic medicinal product hypersensitivity syndrome including DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) and Stevens-Johnson syndrome have occurred in association with rufinamide therapy. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included lymphadenopathy, liver function tests abnormalities, and haematuria. Because the disorder is variable in its expression, other organ system signs and symptoms not noted here may occur. The antiepileptic drug hypersensitivity syndrome occurred in close temporal association to the initiation of rufinamide therapy and in the paediatric population. If this reaction is suspected, rufinamide should be discontinued and alternative treatment started. All patients who develop a rash while taking rufinamide must be closely monitored.
QT shortening
In a thorough QT study, rufinamide produced a decrease in QTc interval proportional to concentration. Although the underlying mechanism and safety relevance of this finding is not known, clinicians should use clinical judgment when assessing whether to prescribe rufinamide to patients at risk from further shortening their QTc duration (eg. Congenital Short QT Syndrome or patients with a family history of such a syndrome).
Women of childbearing potential
Women of childbearing potential must use contraceptive measures during treatment with rufinamide. Physicians should try to ensure that appropriate contraception is used, and should use clinical judgement when assessing whether oral contraceptives, or the doses of the oral contraceptive components, are adequate based on the individual patients clinical situation.
Suicidal ideation
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for rufinamide.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge
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<tr><td>Side Effects</td><td>Very common</td><td>Somnolence, headache, dizziness, nausea, vomiting, fatigue</td></tr>
<tr><td></td><td>Common</td><td>Pneumonia, influenza, nasopharyngitis, ear infection, sinusitis, rhinitis, anorexia, eating disorder, decreased appetite, anxiety, insomnia, status epilepticus, convulsion, coordination abnormal, nystagmus, psychomotor hyperactivity, tremor, diplopia, vision blurred, vertigo, epistaxis, abdominal pain upper, constipation, dyspepsia, diarrhoea, rash, acne, back pain, oligomenorrhoea, gait disturbance, weight decrease, head injury, contusion</td></tr>
<tr><td>Monitoring</td><td colspan="2">Hepatic function
ECG – monitor QT interval
Signs of suicidal ideation and behaviours</td></tr>
<tr><td>Drug Interactions</td><td colspan="2">Rufinamide has the following interaction information:
<table>
<tr><td>Carbamazepine</td><td>plasma concentration of both drugs possibly reduced when rufinamide given with carbamazepine</td></tr>
<tr><td>Fosphenytoin</td><td>plasma concentration of rufinamide possibly reduced by fosphenytoin , also plasma concentration of fosphenytoin possibly increased</td></tr>
<tr><td>Oestrogens</td><td>rufinamide accelerates metabolism of oestrogens (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings)</td></tr>
<tr><td>Phenobarbital</td><td>plasma concentration of rufinamide possibly reduced by phenobarbital</td></tr>
<tr><td>Phenytoin</td><td>plasma concentration of rufinamide possibly reduced by phenytoin , also plasma concentration of phenytoin possibly increased</td></tr>
<tr><td>Primidone</td><td>plasma concentration of rufinamide possibly reduced by primidone</td></tr>
<tr><td>Progestogens</td><td>rufinamide accelerates metabolism of progestogens (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception)</td></tr>
<tr><td>Sodium Valproate</td><td>plasma concentration of rufinamide possibly increased by sodium valproate(reduce dose of rufinamide)</td></tr>
<tr><td>Valproic Acid</td><td>plasma concentration of rufinamide possibly increased by valproic acid (reduce dose of rufinamide)</td></tr>
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Drug Interactions cont…	Rufinamide belongs to **Antiepileptics** and will have the following interactions:	
	Antidepressants, SSRI	anticonvulsant effect of antiepileptics antagonised by SSRIs (convulsive threshold lowered)
	Antidepressants, Tricyclic	anticonvulsant effect of antiepileptics antagonised by tricyclics (convulsive threshold lowered)
	Antidepressants, Tricyclic (related)	anticonvulsant effect of antiepileptics possibly antagonised by tricyclic-related antidepressants(convulsive threshold lowered)
	Antipsychotics	anticonvulsant effect ofantiepileptics antagonised by antipsychotics(convulsive threshold lowered) **Note:** Increased risk of toxicity with myelosuppressive drugs
	MAOIs	anticonvulsant effect of antiepileptics possibly antagonised by MAOIs(convulsive threshold lowered) **Note:** For interactions of reversible MAO-A inhibitors (RIMAs) see Moclobemide, and for interactions of MAO-B inhibitors see Rasagiline and Selegiline; the antibacterial Linezolid is a reversible, non-selective MAO inhibitor
	Mefloquine	anticonvulsant effect of antiepileptics antagonised by mefloquine
	Orlistat	possible increased risk of convulsions when antiepileptics given with orlistat

References

Rufinamide SmPC
Rufinamide BNF
NICE CG 137 - The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care

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I agree to participate in this shared care agreement for the treatment of the below named patient with rufinamide for epileptic seizures in Lennox-Gastaut syndrome

General Practitioner
Name (please print)_____Signature _____Date_____

Hospital Specialist/Consultant
Name (please print)_____Signature_____Date_____

Patient's name	Date of birth	Sex	Home Address	Hospital Number
				NHS Number

Please keep a copy of this agreement for your own records and forward the original to the above named Consultant at: